35. (Amended) An isolated mutant, derivative, analog or homolog of EM 1.

Amendments to the claims are indicated in the attached "Marked Up Version of Amendments" (page iii).

REMARKS

Clarification of the status of Claims 11-16

Applicant's Agent would like to thank the Examiner for the helpful conversation with Ms. Joyce C. Hersh on September 20, 2001, clarifying the status of Claims 11-16, which were omitted from the Office Action (paper no. 9). The Examiner stated that Claims 11-16 are rejected due to their dependence on Claim 3, which does not comply with the Sequence Rules. The Examiner further stated that Claims 11-16 would be allowable, if written in independent form.

Applicant has amended Claim 3 to comply with the Sequence Rules. Since Claim 3, as amended, is allowable, Claims 11-16 are allowable without amending to independent form.

Restriction Requirement

Applicant's Attorney, Ms. Doreen M. Hogle, elected Group II, Claims 2-4, 11-16 and 35 with traversal via voice mail message to the Examiner on March 9, 2001. Applicant's Agent would like to thank the Examiner for reconsideration of the Restriction Requirement and rejoinder of Claim 1 with the claims of Group II, in view of Applicant's traversal of Restriction Requirement, mailed to the U.S. Patent and Trademark Office on June 21, 2001.

Objections to the Specification

The Examiner has objected to the abstract of the disclosure because it is not in compliance with Rule 37 CFR 1.72(b).

Applicant has revised the abstract to recite in narrative form the subject matter of the application. Support for the revision can be found throughout the application, for example, page 9, line 13-25. No new matter has been added by these amendments.

The Examiner also states "[t]he application fails to comply with the sequence requirements of 37 CFR 1.821-1.825, as claims 1, 3, and 4 do have required SEQ ID NO: (Office Action, page 5).

Claim 1 has been cancelled. Claim 3 has been amended to recite SEQ ID NO: 24, and Claim 4 has been amended to recite SEQ ID NO: 25. A Substitute Sequence Listing containing SEQ ID NO: 24 and SEQ ID NO: 25, is attached herein. The Specification has been amended on page 3, line 24, page 3, line 27, and page 11, line 14 to reflect this change. No new matter has been added by these amendments.

The Specification has been amended on page 9, line 28 to correct a typographical error and recite collagen XVIII. Support for this amendment is found throughout the Specification, for example, in Figure 1. No new matter has been added by these amendments.

Rejection of Claims 2 and 35 under 35 U.S.C. §112, Second Paragraph

Claims 2 and 35 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner states that "Claim 2 is drawn to isolated EM1, which comprises a mutated endostatin protein" and that "[r]ecitation of 'EM1' without delineation of the full name of the entity, which the abbreviation denotes is indefinite" (Office Action, page 5).

Applicant respectfully disagrees. The M.P.E.P. at §2173.05(a) states that applicants are "required to make clear and precise the terms that are used to define the invention whereby the metes and bounds of the claimed invention can be ascertained." Applicant discloses on page 9, lines 26-27, that "EM1 is a deletion mutant of endostatin, where the last nine amino acid residues have been deleted." Additionally, the nucleotide sequence (SEQ ID NO: 1) and amino acid sequence (SEQ ID NO: 2) are disclosed. Therefore, the metes and bounds of EM1 are clearly defined, as required under 35 USC §112, second paragraph. Furthermore, the M.P.E.P. at §2173.01 states that "applicants are there own lexicographers" and that they can define the claims in whatever terms they choose "so long as the terms are not used in ways that are contrary to accepted meaning in the art."

The Examiner states that "Claim 35 is drawn to an isolated mutant, derivative, analog, or homolog of EM1" and that "[i]t is indefinite in the recitation of 'derivative, analog, or homolog' as the metes and bounds for what modifications of EM1 may constitute a derivative, analog, or homolog." The Examiner further states that "[a] broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired." The Examiner also states that "claim 35 recites the broad recitation an isolated mutant, derivative, analog, or homolog of the EM1, and the claim also recites the EM1 of claim 2 which is the narrower statement of the range/limitation" (Office Action, page 6).

Claim 35 has been amended to recite an isolated mutant, derivative, analog or homolog of EM1. Thus, the recitation of the EM1 of Claim 2 has been eliminated. Applicants disclose in the Specification on page 17, lines 22-38, that by mutant of EM1 is meant "a polypeptide that includes any changes in the amino acid sequence relative to the amino acid sequence of the reference polypeptide; on page 21, lines 4-5, that by derivative of EM1 is meant "a subject polypeptide having one or more residues chemically derivatized by reaction of a functional side group; on page 18, lines 3-5, that by anolog of EM1 is meant "a non-natural molecule substantially similar to either the entire EM1 molecule or a fragment or allelic variant thereof, and having substantially the same or superior biological activity; on page 20, lines 24-25, that by homolog of EM1 is meant "two sequences which share sequence homology." Therefore, the metes and bounds of derivatives, analogs and homologs of EM1 are defined, as required under 35 USC §112, second paragraph.

Reconsideration and withdrawal of the rejection is respectfully requested.

Rejection of Claim 35 under 35 U.S.C. §112, First Paragraph

Claim 35 is rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner states that "[t]he claim as broadly interpreted is not enabled for the following reasons: The specification provides no guidance or exemplification as to how to make or select

for a derivative, analog, or homolog to EM1 that retains the anti-angiogenic activity of EM1" (Office Action, page 7).

As stated in the M.P.E.P. at §2164, the enablement requirement of 35 USC §112, first paragraph, requires that the specification describe how to make and use the invention. The standard for determining whether the specification meets the enablement requirement has been stated in the courts as follows:

> "The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Applicant respectfully submits that one of ordinary skill in the art would be able to make and use the invention commensurate with the scope of the claims, based upon the teachings disclosed in the Specification and that which is well-known in the art.

Applicant teaches that inhibiting angiogenesis inhibits tumor growth. Applicant further teaches that angiogenesis is characterized by the formation of new blood vessels and includes localized breakdown of the basement membrane lying under the individual endothelial cells, proliferation of those cells, migration of the cells to the location of the future blood vessel, reorganization of the cells to form a new vessel membrane, cessation of endothelial cell proliferation, and, incorporation of pericytes and other cells that support the new blood vessel wall (page 15, line 22, through page 16, line 6). Thus, a number of different assays are relevant to assaying the "anti-angiogenic activity" of a composition. These include assays for inhibition of proliferation of endothelial cells (provided in Example 7, page 52, line 18 to page 53, line 18; Example 10, page 56, lines 1-27), inhibition of migration of endothelial cells (provided in Example 8, page 53, line 20 to page 54, line 31), inhibition of angiogenesis (via the CAM (chorioallantoic membrane) assay, provided in Example 9, page 55, lines 1-29), inhibition of primary renal tumor growth (provided in Example 11, page 57, line 1 to page 58, line 12), activation of apoptosis of endothelial cells (via Annexin V assay, provided in Example 13, page 59, line 9 to page 60, line 30; via Caspase 3 assay, provided in Example 14, page 61, line 1 to 62, line 9; and via microscopic tunnel assay, provided in Example 15, line 10 to page 63, line 28). These assays are commonly used in the field of anti-angiogenic research, and known to those of

ordinary skill in the field. Applicant has therefore provided adequate guidance to evaluate the anti-angiogenic activity of candidate molecules.

Claim 35 has been amended to recite an isolated mutant, derivative, analog or homolog of EM1. As described above, Applicant has clearly defined the metes and bounds of a mutant, a derivative, an analog and a homolog of EM1. Furthermore, Applicant provides guidance and exemplification of how to make endostatin mutants (Examples 2-4) and how to select mutants that retain anti-angiogenic activity (Examples 7-15). Surprisingly, Applicant determined that endostatin mutant, EM1, retains anti-angiogenic activity, whereas endostatin mutant, EM2, does not (Figure 20). Thus, Applicant has made mutant proteins and shown how to select mutant proteins that retain anti-angiogenic activity. Therefore, at a minimum, Claim 35 is enabled for isolated mutants of EM1.

Applicant discloses in the Specification, on page 21, lines 3-17, that EM1 derivatives can have one or more residues chemically derivatized by reaction of a functional side group and provides examples of how to make such compounds. For example, Applicant states in the Specification on page 21, lines 10-11, that "[f]ree hydroxyl groups may be derivatized to form O-acyl or O-alkyl derivatives." Thus, Applicant provides sufficient guidance to make derivatives. As stated above, Applicant teaches how to test candidate molecules, such as mutants, derivatives, analogs and homologs of EM1, for anti-angiogenic activity.

Applicant notes that it is well within the ability of one of ordinary skill in the art to utilize Applicant's teachings described above and routine methods, to select mutants, derivaties, analogs and homologs of EM1 that retain anti-angiogenic activity. Moreover, the M.P.E.P. at § 2164.01, states "[a] patent need not teach, and preferably omits, what is well known in the art." (citing *In re Buchner*, 929 F.2d 660, 661, 18 U.S.P.Q.2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); *Lindemann Maschinen-fabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 U.S.P.Q. 481, 489 (Fed. Cir. 1984)).

Many compounds are routinely altered in the course of practicing the pharmaceutical arts, *e.g.*, proteins and peptides are "PEGylated" to increase their circulatory half-life, amino acids residues are added to increase recombinant production, proteins are chemically modified to allow addition of other molecules, etc. To require Applicant to teach all such methods to protect the

claimed subject matter would be requiring Applicant to teach what is well known, and would give copyists free rein to avoid infringement by making insignificant changes in the claimed anti-angiogenic proteins and peptides.

Furthermore, Applicant is not required to provide working examples of each and every embodiment, and as stated in the M.P.E.P. at § 2164.02,

> The presence of only one working example should never be the sole reason for rejecting claims as being broader than the enabling disclosure, even though it is a factor to be considered along with all the other factors. To make a valid rejection, one must evaluate all the facts and evidence and state why one would not expect to be able to extrapolate that one example across the entire scope of the claims.

Applicant has taught that, surprisingly, a mutant (*i.e.*, SEQ ID NO:2) of endostatin can have anti-angiogenic activity, an important property which was not previously alluded to in the art. Based on Applicant's teachings (*i.e.*, source materials, primer sequences, methods of production, methods of testing, etc.) and routine methods, one of ordinary skill in the art can use Applicant's teaching to produce mutants, derivatives, analogs, and homologs of EM1, and test them for anti-angiogenic activity. Applicant should be entitled to full protection of this invention, which would include further mutants, derivatives, analogs, and homologs of the disclosed anti-angiogenic sequences.

The Examiner cites a number of references to show that the field of protein biochemistry is unpredictable, that "even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein" and that "[c]ertain positions in the sequence are critical to the three dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or no substitutions" (Office Action, pages 7-8).

It appears that the Examiner may be requiring Applicant to reveal details regarding secondary structure of the proteins, *e.g.*, protein folding, binding sites, etc. This is not proper, given that the Examiner has provided neither evidence nor argument that any such showing is

necessary in order for one of ordinary skill in the art to practice the invention, nor has the Examiner pointed to any of Applicant's data as indicating that any such secondary structure, or knowledge of such structure, is needed to inhibit angiogenesis with these molecules.

It is well-established that an Applicant for patent need not comprehend the scientific principles upon which the practical effectiveness of the invention rests (*Cross v. Iizuka*, 753 F.2d 1040, 224 U.S.P.Q. 739 (Fed. Cir. 1985)), rather, an applicant need only demonstrate that the invention as claimed does work. As discussed above, Applicant has made endostatin mutants, and confirmed the anti-angiogenic activity of EM1 by experimental evidence, using methods disclosed in the Specification. The present disclosure provides ample evidence that the invention performs as claimed.

The Examiner has also stated that the Specification "fails to teach what deletions, truncations, substitutions and mutations of the disclosed sequence can be tolerated that will allow the protein to function as claimed" (Office Action, page 8).

The Examiner appears to believe that the activity of any and all protein mutations and amino acid substitutions must be predicted by or predictable from the Specification, apparently absent any testing or screening of that mutation or fragment, in order for that Specification to be enabling for the protein sequence.

However, absolute predictability of the activity of embodiments which may be embraced within the claims is a not a requirement of the statute. The decision in *In re Angstadt*, 190 U.S.P.Q. 218 (C.C.P.A. 1976) clearly states that every embodiment need not be disclosed, even in an unpredictable art, and clearly permits the presence of a screening step to identify those embodiments which possess the desired activity. In fact, in *Angstadt*, the Court specifically dismissed the notion that the specification must provide a level of guidance that would predict the outcome of an experiment (or reaction) "with reasonable certainty before performing the reaction" and that "such a proposition is contrary to the basic policy of the Patent Act, which is to encourage disclosure of inventions and thereby to promote progress in the useful arts."

The Federal Circuit has also stated that

> . . . we do *not* imply that patent applicants in art areas currently denominated as 'unpredictable' must never be allowed generic claims encompassing more than

> the particular species disclosed in their specification. It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art.

In re Vaeck, 947 F.2d 731, 20 U.S.P.Q.2d 1438, 1445 (Fed. Cir. 1991), citing *In re Angstadt*, 537 F.2d 498, 502-3, 190 U.S.P.Q. 214, 218 (C.C.P.A. 1976), emphasis original.

In addition, the Federal Circuit has stated that "[w]hat is patented is not restricted to the examples, but is defined by the words in the claims if those claims are supported by the specification in the manner required by 35 U.S.C. §112." (*Specialty Composites v. Cabot Corp.*, 845 F.2d 981, 6 U.S.P.Q.2d 1601 (Fed. Cir. 1988), at 1604).

The Federal Circuit has also held that claims may encompass some inoperative species, so long as the number of inoperative species does not become significant and force one of ordinary skill into undue experimentation in order to practice the invention (*Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 224 U.S.P.Q. 409 (Fed. Cir. 1984)).

Furthermore, because methods of making mutants, derivatives, analogs and homologs are well known, Applicant is not required to disclose working examples for each. As stated by the M.P.E.P. at § 2164.01(b),

> As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Failure to disclose other methods by which the claimed invention may be made does not render a claim invalid under 35 U.S.C. 112. *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 1533, 3 USPQ2d 1737, 1743 (Fed. Cir.), cert. denied, 484 U.S. 954 (1987).

It is therefore well settled that under 35 U.S.C. § 112, first paragraph, absolute predictability is not required, the claims may encompass some inoperative species, and that some experimentation is permitted. This implicitly permits the absence of absolute predictability of each claimed embodiment. Thus, the present specification enables the claimed invention,

without undue experimentation. The rejection, based upon the assumption that the specification must teach those specific mutations, derivaties, analogs and homologs which will encode an active protein, is in error.

Applicant notes that it is neither cumbersome nor costly to test mutants, derivatives, analogs, and homologs of EM1 for use in the invention. Time and expense are merely factors in the consideration of undue experimentation, they are not controlling factors (*United States v. Telectronics Inc.*, 857 F.2d 778, 785, 8 U.S.P.Q. 2d 1217, 1223 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1998). In *In re Wands*, the court stated that "[e]nablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. 'The key word is 'undue' not 'experimentation' ' " (citing *In re Angstadt*, 537 F. 2d 498 at 504, 190 U.S.P.Q. 214 at 219 (C.C.P.A. 1976)). The Court also stated that "the test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." (citing *In re Jackson*, 217 U.S.P.Q. 804 at 807 (Bd. App. 1982)).

In summary, Applicant's disclosure provides adequate guidance and exemplification of how to make and evaluate the anti-angiogenic activity of candidate molecules use the claimed invention, as required under 35 U.S.C. §112, first paragraph.

Applicant respectfully submits that the teachings disclosed in the specification fully enable one of ordinary skill in the art to make and/or use the invention commensurate in scope with the claims, without undue experimentation. Reconsidered and withdrawal of the rejection are respectfully requested.

Rejection of Claim 1 under 35 U.S.C. §102

Claim 1 is rejected under 35 U.S.C. §102(b) as being anticipated by Oh, *et al.*, (1995). The Examiner states that "[t]he claims are drawn to an isolated anti-angiogenic peptide, wherein the C-terminus comprises the amino acid sequence SYIVLCIE." The Examiner further states that "Oh, *et al.* teach an amino acid sequence comprising the endostatin protein, which may be

useful in the treatment of solid tumors, thus indicating its anti-angiogenic capabilities," and that, "[t]herefore, the prior art references teaches the as claimed" (Office Action, page 8).

While not agreeing with the Examiner, and solely to speed prosecution, Applicant has canceled Claim 1. Applicant respectfully requests the rejection be withdrawn.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 341-0036.

Respectfully submitted,

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Dated: March 11, 2002

MARKED UP VERSION OF AMENDMENTS

Specification Amendments Under 37 C.F.R. § 1.121(b)(1)(iii)

Replace the paragraph at page 3, lines 22 through 30 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

The invention relates to the discovery of an isolated anti-angiogenic peptide, wherein the C-terminal end of the peptide comprises the amino acid sequence SYIVLCIE (SEQ ID NO: 24), which has anti-angiogenic properties. Designated "EM 1," this protein comprises a mutated endostatin protein, where the mutation comprises a deletion of nine consecutive amino acids from the C-terminus of the mutated endostatin protein (*e.g.*, NSFMTSFSK (SEQ ID NO: 25)). EM 1 terminates in the amino acid sequence SYIVLCIE (SEQ ID NO: 24). The invention also comprises isolated polynucleotides encoding EM 1, operably linked to expression sequences, and host cells transformed with such a construct. Antibodies to EM 1 are also disclosed.

Replace the paragraph at page 9, line 26 through page 10, line 2 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

Specifically, EM 1 is a deletion mutant of endostatin, where the last nine amino acid residues have been deleted. EM 1 exists naturally as part of the collagen Type XVIII molecule, but it can be produced recombinantly, *e.g.*, the polynucleotide sequence (Fig. 1, SEQ ID NO:1) encoding EM 1 protein (Fig. 2, SEQ ID NO:2) can amplified, *e.g.*, with the forward and reverse primers listed in Table 1, below. The template nucleic acid used for the amplification can be from any mammal. Also encompassed by the present invention is mammalian EM1, fragments, mutants, derivatives or fusion proteins thereof.

Replace the paragraph at page 11, lines 8 through 22 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

The resulting amplification product can then be cloned into a suitable vector. The term "primer" denotes a specific oligonucleotide sequence complementary to a target nucleotide sequence and used to hybridize to the target nucleotide sequence and serve as an initiation point for nucleotide polymerization catalyzed by either DNA polymerase, RNA polymerase or reverse transcriptase. "EM 1," as used herein, refers to a deletion mutant of endostatin, wherein the last nine amino acid residues have been deleted (*i.e.*, NSFMTSFSK (SEQ ID NO: 25)), and the term is intended to include fragments, mutants, homologs, analogs, and allelic variants of the amino acid sequence of SEQ ID NO:2). Although EM 1 was originally cloned from mouse nucleic acid, it performs better than intact type endostatin (*i.e.*, endostatin that has not been mutated) in standard assays. The term EM 1 is therefore intended to include any mammalian sequence substantially similar to EM 1 as described herein, as well as mammalian EM 1 fragments, mutants, homologs, analogs and allelic variants of the mammalian EM 1 amino acid sequence. Also, specifically encompassed by the present invention are human endostatin mutants, and more specifcally, the human deletion mutant equivalent of EM 1.

Replace the paragraph at page 71, line 3 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

[Anti-angiogenic peptides and methods of use are described.] EM 1, a novel anti-angiogenic protein, and a deletion mutant of endostatin, is described, as well as methods of making EM1, therapeutic compositions comprising EM1, and methods for using those compositions.

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

3. (Amended) The isolated EM1 of Claim 2, wherein the C-terminus of the isolated EM 1 comprises [the amino acid sequence SYIVLCIE] SEQ ID NO: 24.

4. (Amended) The isolated EM 1 of Claim 2, wherein the deletion of nine consecutive amino acids comprises [the amino acid sequence NSFMTSFSK] SEQ ID NO: 25.

35. (Amended) An isolated mutant, derivative, analog or homolog of [the] EM 1 [of Claim 2].